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CYCLOSPORIN – INDUCED REMISSION IN AN INFANT WITH ALKYLATING AGENTS – RESISTANT NEPHROTIC SYNDROME*

A Case Report

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SUMMARY: Yılmaz GG, Gür GÜven A. (Nephrology Unit, Department of Pediatrics, Akdeniz University Faculty of Medicine, Antalya, Turkey). Cyclosporin-induced remission in an infant with alkylating agents-resistant nephrotic syndrome: a case report. Turk J Pediatr 1995; 37: 411-414.

The efficacy of cyclosporin-A, a potent immunosuppressive agent, has not been clearly proven in the management of childhood nephrotic syndrome. The occurrence of early relapse as the dose of cyclosporin is tapered or as soon as the drug is stopped and the potential nephrotoxic effects of prolonged treatment have caused it to be used in limited cases. We report an eighteen-month-old boy with steroid toxicity and alkylating agents-resistant nephrotic syndrome, who subsequently went very quickly into remission lasting at least one year after receiving cyclosporin-A for only three months. *Key words: nephrotic syndrome, steroid toxicity, alkylating agents resistance, cyclosporin-A.*

Achieving sustained remission with minimum drug-induced adverse effects is the goal of therapy in the management of idiopathic nephrotic syndrome (INS). When basic corticosteroid treatment fails or symptoms of steroid toxicity appear, immunosuppressive drugs must be used. Traditionally, alkylating agents (AA) have been the first choice. The efficiency of AA in preventing further relapses and inducing prolonged remissions has been proven by prospective and retrospective studies[1-4]. Cyclosporin-A (CyA) is a new drug which has been used in the treatment of INS during the last ten years[5]. Both therapy regimens have numerous side effects. CyA can also cause nephrotoxicity, which can be suspected by abnormal renal functional tests or identified histopathologically. Other side effects of CyA are moderate elevation of blood pressure, hyperkalemia, hypomagnesemia, gum hypertrophy and hypertrichosis[6]. Detailed knowledge about the effectiveness and safety of the drug, as well as precise indications and duration of treatment in various clinical and histological forms of INS have not been clearly described.

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Case Report

An eighteen-month-old boy was admitted with intractable generalized edema. Five months previously he had been diagnosed with INS and treated with corticosteroids (Prednisolone) at a dosage of 2 mg/kg/day for four weeks. Remission was achieved, but when the dose was tapered he relapsed. His clinical nephrotic picture, mainly edema, deteriorated despite taking steroids irregularly for three months. On admission to our unit, prednisolone was readministered at 2 mg/kg/day. Proteinuria decreased to 1+ in ten days, but a relapse occurred when the prednisolone was tapered to 1 mg/kg/day. He was hypertensive, and his serum albumin was 1.3 g/dl. Edema was so prominent on his eyelids that he could not open his eyes. Urinary tract infection, sinusitis and oral moniliasis ensued, and steroids had to be withdrawn. Cyclophosphamide was prescribed at 2.5 mg/kg/day for eight weeks with no benefit. In the meantime, several infusions of human albumin and diuretics were given with no effect. The decision was made to follow him with general supportive treatment and no medication. Renal biopsy was performed, revealing glomerular changes compatible with minimal lesion nephrotic syndrome. His generalized and disturbing edema, hypertension and massive proteinuria did not change despite another course of therapy with the second alkylating agent, chlorambucil, at a dose of 0.2 mg/kg/day for five weeks. Subsequently CyA was started at 7 mg/kg/day. The proteinuria diminished within three days. On the tenth day of therapy the edema and proteinuria dramatically disappeared. The dose of CyA was manipulated between 3-6 mg/kg/day, maintaining the blood level at 43-97 ng/ml (with RIA). Since he was in complete remission, the dose was not increased and was stopped at the end of three months. Serum creatinine levels were 1.1 mg/dl and 0.5 mg/dl before and after CyA therapy, respectively. The patient remained in remission for eleven months after cessation of CyA. No biochemical or clinical side effects were observed during or after CyA therapy.

Discussion

Corticosteroids are introduced as standard therapy when the diagnosis of INS is made, with or without a kidney biopsy[7]. However, at least seven to 15 percent of children with INS are resistant to therapy[8]. Some of them show steroid dependency and/or toxicity related with variable individual components and with the cumulative doses. In many of these patients, a short course of cyclophosphamide or chlorambucil can achieve a stable remission[3,4,6]. But alkylating agents also have cumulative toxicity[8,9].

In our case, the initial therapy with corticosteroids sustained a short remission. Subsequently, the patient presented with steroid dependency, and adverse effects of steroids such as bacterial and fungal infections and hypertension were

observed. We were concerned that this patient would not be a good candidate for alkylating agents. These drugs are known to be more effective in older children, in frequent relapsers, when given in the remission period and combined with full-dose steroids[6].

The poor clinical outcome of our patient despite additional albumin and diuretic infusions, persistent generalized edema, and long-lasting massive proteinuria led us to give cyclophosphamide and chlorambucil, one after the other. When these treatments failed, the new drug, CyA, which has been used in last ten years in the treatment of INS, was introduced to our patient. A dramatically rapid and complete remission was obtained.

A one-year sustained remission following a three-month course of CyA treatment encouraged us to report this experience. The indications and mode of therapy with CyA in various clinical and histopathological forms of INS have not yet been established. Its effect is based on two postulates: first, INS is presumably an immunologically-based disorder; and second, CyA exerts its immunomodulator effect on T-cell immunity. CyA also changes the properties of the glomerular barrier, resulting in increased charge and size selectivity, and diminishes the proteinuria[10, 11].

The first experience in children treating with CyA was reported by Hoyer et al.[12]. Thereafter, Capodicasa et al.,[13] Tejani et al.,[14] Niaudet et al.[15] and others showed that 80 percent of children with NS can be maintained in remission with CyA. CyA is also effective in patients with frequent relapses, as in steroid-dependent nephrotics, but less encouraging results have been reported in steroid-resistant patients and those with focal glomerular sclerosis[13-15]. It has been reported that alkylating agents can be more effective than CyA in steroid-dependent INS[16].

There is some concern over the duration of treatment, since relapses may occur when CyA is tapered or stopped[14, 15, 17, 18]. Relapse can occur immediately or one to ten months after cessation of therapy. Although two months to 5.2 year periods have been reported, a three or four-month course seems to be the preferred duration of therapy[14, 17, 19].

The long-term tolerance of CyA has been investigated[19]. The drug has nephrotoxic and other (hypertension, hypertrichosis, gum hypertrophy, hyperkalemia, hypomagnesemia) side effects, and many factors must be considered for the safe and effective use of the drug[5].

In conclusion, patients with minimal-change nephrotic syndrome can successfully be treated with CyA even after former failure of therapy with steroids and alkylating agents. In our case, remission was achieved in a very short time and sustained at least a year following a relatively short duration of therapy.

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